Chronic diarrhoea in children

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9

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Alfredo Guarino, MD, Professor *, Andrea Lo Vecchio, MD, PhD, Student, Roberto Berni Canani, MD PhD, Professor

Department of Pediatrics, University of Naples Federico II, Via S. Pansini 5, Naples, Italy

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A B S T R A C T

Chronic diarrhoea in children shows an age related spectrum. In infants and young children a major role is related to persistent intestinal infections, intolerance to specific nutrients such as cow's milk protein, and toddler's diarrhoea. In older children and adolescents, inflammatory bowel diseases are strongly increasing and nonspecific diarrhoea is also frequent. Coeliac disease is a major cause of diarrhoea throughout childhood. In neonates, congenital diarrhoea is a rare but severe syndrome that includes several highly complex diseases. In children, diagnosis should be based on noninvasive techniques. Endoscopy should be decided based on clinical criteria, but also driven by noninvasive tests to assess the digestive absorptive functions and intestinal inflammation. A stepwise approach may reduce the need of endoscopy, also in the light of its relatively limited diagnostic yield compared to adult patients. Treatment of chronic diarrhoea in children is also substantially different from what is generally done in adults and includes a major role for nutritional interventions. Therefore chronic diarrhoea in children is a complex age-specific disorder that requires an age-specific management that is in many aspects distinct from that in adults.

Introduction

Chronic diarrhoea refers to the persistence of loose stools (generally with an increase in stool frequency) for at least 14 days [1]. Definitions such as 'persistent' or 'protracted' diarrhoea are less

* Corresponding author. Tel.: +39 0817464232.
E-mail address: alfguari@unina.it (A. Guarino).

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consistent in terms of duration, and generally refer to an acute-onset diarrhoea that runs a course longer than expected.

The etiologic spectrum of chronic diarrhoea in children is substantially different from that observed in adults and changes with age even within infancy and childhood. Diarrhoea associated with cancer is extremely rare in childhood, whereas – conversely-congenital diarrhoea occurs exclusively in early infancy. Several diseases are common to adults and children, but may have different definitions and presentations. The best example is chronic nonspecific diarrhoea, which is the paediatric counterpart of the functional diarrhoea in adults. According to the Rome III criteria, chronic nonspecific diarrhoea is defined as toddler's diarrhoea in children younger than four years and as irritable bowel syndrome in the age range of 5–18 years; the two definitions are rather distinct [2]. Also the clinical hallmarks of chronic diarrhoea may be different in adults and children, who require an age-targeted approach. In addition, the diagnostic work up in children is hampered by the need to limit invasive procedures and by the interpretation of reported symptoms, which may be difficult in young children.

In this paper we present the main features of childhood diarrhoea and suggest a stepwise diagnostic approach, which includes noninvasive intestinal function tests. The use of the latter may limit unnecessary endoscopic procedures thereby resulting in less stressful management of children. We also describe congenital diarrhoeal disorders, a group of severe and rare conditions that are specific to early infancy and require a tertiary care centre for diagnosis and treatment [3].

The aetiology of chronic diarrhoea in children

The main causes of chronic diarrhoea in children are listed in Table 1. The aetiology of chronic diarrhoea is strongly determined by socio-economic factors and by the clinical setting. In developing countries, chronic diarrhoea is frequently caused by infections; malnutrition is a major risk factor for a protracted course [4]. The most common etiologies of chronic diarrhoea in developed countries are functional intestinal disorders, nutrient malabsorption, and inflammatory bowel diseases (IBD), but persistent infections of the intestinal tract are also common. There are also many other less common causes of chronic diarrhoea. However, as shown in Table 2, the spectrum of aetiology is largely age-dependent and many conditions are virtually exclusive, or confined to, specific age ranges.

Intestinal infections are always a potential aetiology of chronic diarrhoea and selected agents show a peculiar distribution. Entero-adherent *Escherichia coli* and *Cryptosporidium parvum* have been

Table 1
Main causes of chronic diarrhoea in children.

Infectious aetiologies:
Bacterial, viral and protozoan agents, small intestinal bacterial overgrowth, post-enteritis syndrome, tropical sprue, Whipple disease

Non-infectious aetiologies:
Diarrhoea associated with exogenous substances: Excessive intake of carbonated fluid, dietetic foods containing sorbitol, mannitol or xylitol; excessive intake of antiacids or laxatives containing lactulose or $Mg(OH)_2$; excessive intake of methylxanthines-containing drinks (cola, tea, coffee); NSAIDs.
Abnormal digestive processes: Cystic fibrosis, Shwachman–Diamond syndrome, isolated pancreatic enzyme deficiency, chronic pancreatitis, Johanson–Blizzard Syndrome, Pearson syndrome. Trypsinogen and enterokinase deficiency: chronic cholestasis, use of bile acids sequestrants, primary bile acid malabsorption, terminal ileum resection.
Nutrient malabsorption: Congenital or acquired sucrase-isomaltase deficiency; congenital or acquired lactase deficiency; glucose-galactose malabsorption; fructose malabsorption, congenital or acquired short bowel
Immune/inflammatory: Food allergy; coeliac disease; eosinophilic gastroenteritis, inflammatory bowel diseases, autoimmune enteropathy, primary and secondary immunodeficiencies, IPEX syndrome.
Structural defects: Microvillus inclusion disease, tufting enteropathy, phenotypic diarrhoea, heparan-sulphate deficiency, $\alpha_{2\beta1}$ and $\alpha_{6\beta4}$ integrin deficiency, lymphangiectasia.
Defects of electrolyte and metabolite transport: Congenital chloride diarrhoea, congenital sodium diarrhoea, acrodermatitis enteropathica, selective folate deficiency, abetalipoproteinemia.
Motility disorders: Hirschsprung's disease, chronic intestinal pseudoobstruction (neurogenic and myopathic), thyrotoxicosis.
Neoplastic diseases: Neuroendocrine hormone-secreting tumours: APUDomas (Amine Precursor Uptake and Decarboxylation) such as VIPoma (Vasoactive intestinal polypeptide), Zollinger- Ellison and mastocytosis.
Chronic non-specific diarrhoea: Functional diarrhoea, toddler's diarrhoea, irritable bowel syndrome.

Table 2
Main causes of chronic diarrhoea according to the age of onset.

0–30 Days	1–24 Months	2–18 Years
Abetalipoproteinemia	Apple juice and pear nectar	Apple juice or pear nectar
Acrodermatitis enteropathica	Autoimmune enteropathy	Antibiotic-associated
Autoimmune enteropathy	Chronic infection by *C. difficile*,	*C. difficile* colitis
Congenital chloride Diarrhoea (CLD)	*G. lamblia*	Chronic infection by
Congenital sodium diarrhoea (CDS)	Chronic non-specific diarrhoea	*C. difficile*, *G. lamblia*.
Congenital short-bowel syndrome	Coeliac disease	Coeliac disease
Congenital lactase deficiency	Cystic fibrosis	Irritable bowel syndrome
Disaccharide intolerance	Food allergy	Inflammatory bowel disease
Food allergy	Post-gastroenteritis diarrhoea	Lactose intolerance
Glucose-galactose malabsorption		Post-gastroenteritis diarrhoea
Hirschsprung'sdisease		
Immunodysregulation, polyendocrinopathy and enteropathy		
Lysinuric protein intolerance		
Malrotation with partial blockage		
Microvillous inclusion disease (MID)		
Neonatal lymphangiectasia		
Primary bile-salt malabsorption (PBAM)		
Tufting enteropathy		
Intestinal pseudoobstruction		

implicated in potentially severe chronic diarrhoea in developing countries. In developed countries, chronic infectious diarrhoea usually runs a benign course. *Rotavirus* and *Norovirus* are frequently involved, whereas *Cytomegalovirus* and *Clostridium difficile* are emerging agents of severe diarrhoea in selected populations. Opportunistic microorganisms in specific populations, such as immunocompromised children, can cause chronic and severe diarrhoea. However different conditions are associated with specific microorganisms. Cryptosporidiosis is the most frequent cause of chronic diarrhoea in children with HIV infection who have no access to antiretroviral combination therapy, but HIV virus also may be directly responsible for diarrhoea and for the so called HIV-enteropathy through a direct effect on the enterocyte involving a redox – mediated mechanism [5–7]. An entirely different pattern of agents is found in IBD and several enteric agents may trigger relapses in these children (Table 3).

A common syndrome of chronic diarrhoea is small intestinal bacterial overgrowth, in which diarrhoea may be the result of either a direct microorganism/enterocyte interaction or the consequence of deconjugation and dehydroxylation of bile salts, and hydroxylation of fatty acids due to an abnormal proliferation of bacteria in the proximal intestine. Bacterial overgrowth may be difficult to detect as hydrogen breath test is still poorly standardized in children [8]. Postenteritis syndrome is a clinical-pathological condition in which diarrhoea persists following an acute onset intestinal infection.

Table 3
The etiologic spectrum of chronic diarrhoea is completely different children with AIDS.

Children with AIDS	Children with IBD
• *Cryptosporidium*	• *Clostridium difficile*
• *Clostridium difficile*	• Aeromonas
• *Cytomegalovirus*	• Campylobacter
• *Campylobacter* spp.	• *E. coli* O157:H7
• *Entamoeba histolytica*	• Giardia lamblia
• *Enteric viruses*	• Plesiomonas
• *Giardia lamblia*	• Salmonella
• *Isospora belli*	• Shigella
• *Mycobacterium avium intracellulare*	• Yersinia
• *Microsporidia*	• Adenovirus
• *Salmonella* spp.	• Cytomegalovirus
• *Shigella* spp.	• Rotavirus (group A)
• *Strongyloides*	
• *HIV virus*	

Sensitization to food antigens, secondary disaccharidase deficiency reinfections or a change in the microbiota may be responsible for postenteritis syndrome.

A reduction of intestinal absorptive surface is responsible for diarrhoea in coeliac disease, a genetic intolerance to gluten that affects as many as one in 100 normal subjects, depending on geographic origin. Gluten intolerance causes villous atrophy leading to a reduction of functional absorptive surface area that is reversible upon gluten free diet.

Food allergies may present with chronic diarrhoea through a non-IgE-mediated mechanism, especially during infancy [9]. Eosinophilic gastroenteritis is characterized by eosinophilic infiltration of the intestinal wall and is strongly associated with atopy.

In older children and adolescents, inflammatory bowel diseases (IBD), including Crohn's disease, ulcerative colitis and indeterminate colitis, are major causes of chronic diarrhoea.

Chronic diarrhoea may be the manifestation of maldigestion due to exocrine pancreatic disorders. In most patients with cystic fibrosis, pancreatic insufficiency results in fat and protein malabsorption. In Shwachman–Diamond syndrome, exocrine pancreatic hypoplasia may be associated with neutropenia, bone changes, and intestinal protein loss. Specific pancreatic enzyme defects result in fat and/or protein malabsorption. Familial pancreatitis associated with a mutation in the trypsinogen gene may be associated with pancreatic insufficiency and chronic diarrhoea.

Liver disorders may lead to a reduction in the bile salts resulting in fat malabsorption. Bile acid loss may be associated with terminal ileal diseases, such as Crohn's disease or following ileal resection. In primary bile acid malabsorption, neonates and young infants present with chronic diarrhoea and fat malabsorption due to mutations of ileal bile transporter.

The most benign aetiology of chronic diarrhoea in children is chronic non-specific diarrhoea which encompasses functional diarrhoea (or toddler's diarrhoea) in subjects below four years of age and irritable bowel syndrome in those aged 5–18 years [2]. The disease is the same, but presentation varies with age: abdominal pain is more frequent and clearly associated with diarrhoea in older than in younger children (Table 4). The hallmark of the syndrome is diarrhoea associated with normal weight growth in well-appearing subjects.

Table 4
Age-related Rome III criteria for functional diarrhoea.

Age	Criteria
Neonate and Toddlers (below 4 years): diagnostic criteria for functional diarrhoea	1. Daily painless, recurrent passage of three or more large, unformed stools; 2. Symptoms that last more than four weeks; 3. Onset of symptoms that begins between 6 and 36 months of age; 4. Passage of stools that occurs during waking hours; 5. There is no failure-to-thrive if caloric intake is adequate
Child and Adolescent (5 to 18 years): diagnostic criteria[a] for irritable bowel syndrome	1. Abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with two or more of the following at least 25% of the time: a) Improved with defecation b) Onset associated with a change in frequency of stool c) Onset associated with a change in form (appearance) of stool 2. No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the subject's symptoms
Adults (older than 18 years): diagnostic criteria[b] for irritable bowel syndrome	Recurrent abdominal pain or discomfort[c] at least three days per month in the last three months associated with two or more of the following: 1. Improved with defecation 2. Onset associated with a change in frequency of stool 3. Onset associated with a change in form (appearance) of stool

[a] Criteria fulfilled at least once per week for at least two months before diagnosis.
[b] Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis.
[c] Discomfort means an uncomfortable sensation not described as pain. In pathophysiology research and clinical trials, a pain/discomfort frequency of at least 2 day a week during screening evaluation for subject eligibility.

The most severe etiologies of chronic diarrhoea include a number of heterogeneous conditions called congenital diarrhoeal disorders (CDD) that often present in newborns [3,10,11]. Selected causes of CDD lead to the intractable diarrhoea syndrome, which is often the result of a defect in the structure of the intestine or of the enterocyte, leading to progressive, often irreversible intestinal failure, which requires parenteral nutrition for survival.

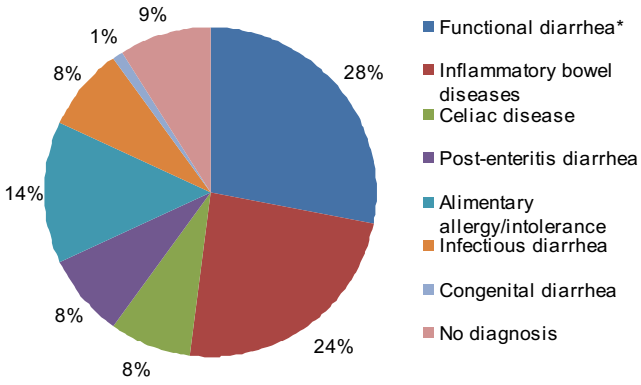
The approach to children with chronic diarrhoea is strongly driven by the clinical setting and the patient population. Fig. 1 shows the pattern of aetiology of a population of children seen at a referral centre.

Diagnostic approach to the child with chronic diarrhoea

Similar to adults, endoscopy and histology are often crucial in the diagnostic approach. However, in children it is important to minimize the invasive tests. Evaluation of a child with chronic diarrhoea should start with four main clinical features: the age of the child, pattern of weight loss or gain, the character of the stools (i.e. watery malabsorptive, inflammatory) and any associated symptoms. A careful history and physical examination are the cornerstones of diagnostic approach, including the age of onset, and whether it was abrupt or gradual. These clinical features are used to plan a diagnostic algorithm.

A family history is important to assess the possibility of inherited conditions. Most infants and children with food allergy come from atopic families, and commonly the parents themselves had vomiting and diarrhoea when exposed to particular foods in childhood. Many infants and children with coeliac disease come from families with other affected members or have relatives with dermatitis herpetiformis. Other inherited conditions are cystic fibrosis and IBD. Many CDD conditions (i.e. microvillous inclusion disease) are associated with consanguinity.

A major issue in the initial approach is growth and nutritional assessment. Although there are many ways to perform a nutritional assessment, weight for height is the simplest index of growth failure secondary to malnutrition. Sequential height and weight records, with measurement of head circumference, are critical to determine whether, and to what extent, the disease has impaired growth. Height is generally involved later than weight in chronic diarrhoea and its impairment suggests a long standing condition. The weight curve can range from normal or even excessive growth in diarrhoea due to overfeeding, to an arrest or decrease in malnutrition and stunted growth in conditions such as coeliac disease, and delayed growth velocity and puberty in Crohn's disease. Poor weight gain may be due to malabsorption, low intake, or can be secondary to changes in metabolism, as in hyperthyroidism. Poor growth may be due to feeding a dilute hypocaloric formula or clear liquids in an effort to reduce diarrhoea. Stool features (watery, presence of blood and mucus, presence or absence of undigested food



* Diagnostic approach according to age (Rome III Criteria)

Fig. 1. Main aetiological groups of chronic diarrhoea in population of 354 children consecutively seen at a tertiary care centre of gastroenterology in Europe.

particles, steatorrhoea) may aid in establishing the pathophysiology of diarrhoea which could be secretory, inflammatory, osmotic, malabsorptive, or functional in nature. Stool frequency and volume may aid in establishing the diarrhoea severity. If the patient has been admitted to the hospital and has been electrolyte depleted and dehydrated on one or more occasions, a serious diagnosis should be considered. If a child or a teenager wakes up at night to defecate or becomes incontinent, an organic basis for diarrhoea is likely. The presence of blood and/or mucus in the stools suggests intestinal inflammation and possibly IBD. On the contrary, indicators of a functional aetiology are a long duration of symptoms, the lack of significant weight loss, and absence of nocturnal diarrhoea. The Rome III diagnostic criteria are helpful to make a final diagnosis in these cases (Table 4). Vomiting may indicate intestinal dismotility, due to either mucosal or bowel-wall disease or adhesions from previous surgery, but is frequently a sign of food intolerance or – less frequently – is associated with an extraintestinal conditions, such as urinary tract infection, that may induce diarrhoea. Abdominal distension could be secondary to true obstruction, pseudo-obstruction, malabsorption, or hypersecretion of liquids in the intestine. A review of any systemic or extraintestinal signs and symptoms is useful in search for other diagnostic clues. The presence of fever is more typical of infectious or inflammatory processes. Arthralgias, arthritis, uveitis, pyoderma gangrenosum, and hepatitis are all indications of IBD. Recurrent respiratory tract infections may suggest cystic fibrosis, or immunodeficiency.

In infants with chronic diarrhoea, a thorough feeding history must be obtained. The type of milk formula and the reaction to its initial administration should be determined. If the infant is or was breast-fed when diarrhoea began, a careful history of the mother's diet must be determined, especially looking for any response in the infant's symptoms to changes in the mother's diet. The age at which juice, fruit and gluten-containing products were added should be noted in these infants, and correlated with symptoms. Onset of diarrhoea soon after fruit and juice are added is typical of sucrase-isomaltase deficiency. On the contrary, symptoms of coeliac disease may not develop for weeks, months, or even years after gluten is added to the diet.

The initial approach may provide clues for aetiology and help design a rational plan of investigations. In children with normal weight growth, the most probable cause is functional diarrhoea. However it is important that the conditions meet the age-specific criteria for functional diarrhoea listed in Table 4, in order to obtain a reliable diagnosis. Functional diarrhoea only requires monitoring, and parents need to be reassured of the benign outcome of the condition.

If the stools do not contain occult or gross blood, white blood cells or eosinophils, an inflammatory or food allergy could be reasonably excluded.

Large volumes of loose stools with steatorrhoea indicate nutrient malabsorption or maldigestion. Coeliac disease is the single most frequent cause of chronic malabsorptive diarrhoea; serology (IgA anti-tissue transglutaminase type 2 antibody and endomysial antibodies) is a needed test in children of any age on gluten containing diet, as indicated by current guidelines [12].

In children with weight loss, the diagnostic work up should start with noninvasive tests to evaluate the digestive and absorptive functions and the presence of inflammation (Table 5). Nutrient absorption tests (Table 5A) are generally performed on stools and provide information on the integrity of small bowel functions. Conversely, increased markers of inflammation (Table 5B), reflect intestinal inflammation, which is often of colonic origin. Fecal calprotectin, a protein in neutrophils, is not a colonic specific marker. However if combined with measurement of nitric oxide in the fluid obtained from

Table 5A
Non-invasive tests for intestinal digestive-absorptive functions.

Test	Normal values	Implication
α1-antitrypsin fecal concentration	<0.9 mg/g stool	Increased intestinal permeability/ protein loss
Steatocrit	<2.5% (older than 2 years)	Fecal fat loss, maldigestion
Fecal reducing substances	Absent	Carbohydrates malabsorption
Elastase concentration	>200 μg/g stool	Exocrine pancreatic dysfunction
Chymotrypsin concentration	>7.5 U/g >375 U/24 h	Exocrine pancreatic dysfunction
Dual sugar (cellobiose/mannitol) absorption test	Urine excretion ratio: 0.010 ± 0.018	Increased small bowel permeability

Table 5B
Non-invasive tests for intestinal inflammation.

Test	Normal values	Implication
Fecal occult blood	Absent	Fecal blood loss
Fecal calprotectin concentration	<100 μg/g for children aged >12 m	Intestinal inflammation
Fecal leukocytes	<5/microscopic field	Colonic inflammation
Nitric oxide in rectal dyalisate	<5 μM of NO_2^-/NO_3^-	Localizes inflammation in the rectum

a small bag placed in the rectum (rectal dialysis bag), it quite reliably reflects distal intestinal inflammation [13]. Fecal calprotectin may be therefore a screening test, alone or in combination with other noninvasive tests, to determine if colonoscopy is indicated [14].

Overall, noninvasive tests in chronic diarrhoea provide clues to detect aetiology and plan subsequent diagnostic work up. Generally abnormalities in nutrient absorption tests may indicate a need for upper endoscopy whereas inflammation suggests to proceed with rectosigmoidoscopy or colonoscopy (Fig. 2). The use of noninvasive tests in addition to this stepwise approach (Table 6) strongly reduced the need for invasive investigations and associated costs [15]. While upper or lower endoscopy is often necessary and should be done in conditions of analgesia appropriate for children's age [16], it may not always provide a conclusive diagnosis [17]. Radiology imaging has a role in the diagnostic approach to children with chronic diarrhoea, but is less important than in adults. Abdominal ultrasound may help detecting a thickened distal bowel wall suggesting mucosal disease such as Crohn's disease [14].

Chronic diarrhoea in the neonatal age

Diarrhoea is relatively rare in neonates, but its early onset may be predictive of congenital diarrhoeal disorders that may require hospitalization [10]. Several conditions are related to genetic defects. Thus molecular diagnosis can be helpful also for genetic counselling for the family [18].

Diagnosis depends on determining whether the patient has sufficient functioning bowel for nutrient digestion and absorption. A major issue is to assess whether the intestinal villi are intact or congenitally defective, as in microvillous inclusion disease or in tufting enteropathy; or whether there

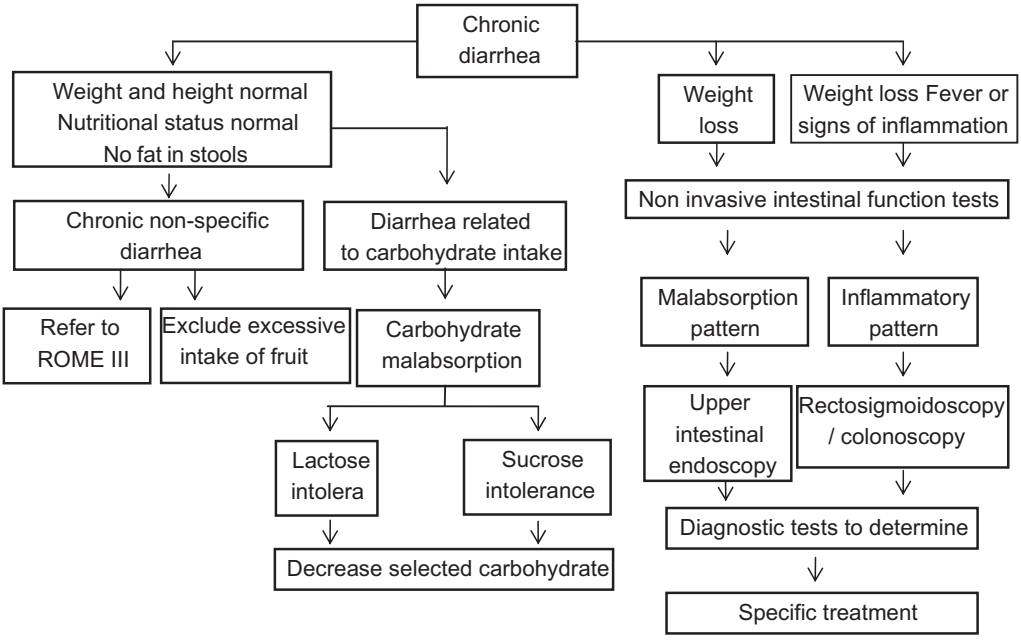


Fig. 2. Diagnostic algorithm for children with chronic diarrhoea.

Table 6
Stepwise diagnostic approach to children with diarrhoea.

Step 1	**Intestinal microbiology** ○ Stool cultures ○ Microscopy for parasites ○ Viruses ○ H_2 breath test
	Screening test for coeliac disease: ○ Serology according to age and level of IgA (including AGA IgA/IgG, EMA IgA/IgG, tTG IgA/IgG)
	Non invasive tests for: ○ Intestinal function (including double sugar test, xylosemia, iron absorption test) ○ Pancreatic function (amylase, lipase, fecal elastase) ○ Intestinal inflammation (fecal calprotectin, rectal nitric oxide)
	Tests for food allergy: ○ Prick/patch tests for foods
	Abdominal Ultrasounds (scan of last ileal loop)
Step 2	**Evaluation of intestinal morphology**: ○ Endoscopy and standard jejunal/colonic histology[a] ○ Morphometry ○ PAS staining ○ Electron microscopy
	Imaging (upper or lower bowel series, capsule endoscopy)
Step 3	**Special investigations**: ○ Intestinal immunohistochemistry ○ Anti-enterocyte antibodies ○ Serum chromogranin and catecholamines ○ Autoantibodies ○ 75SeHCAT measurement ○ Brush border enzymatic activities ○ Motility and electrophysiological studies

[a] The choice of upper and lower endoscopy may be supported by noninvasive tests From Guarino A and Branski D Nelson Textbook of Pediatrics XIX Edition (modified).

is a defect of monosaccharide digestion and absorption, or in Cl^- and Na^+ absorption, as in congenital chloride diarrhoea and congenital sodium diarrhoea, respectively. Some patients need small bowel radiology to assess intestinal length and to look for malrotation. Congenital short-bowel syndrome may present with malabsorption in the absence of inflammatory changes in the stools. If bowel length appears normal, the patient should have small intestinal biopsies to look for characteristic changes seen by light and electron microscopy in primary enterocyte abnormalities. Finally an aliquot of intestinal fluid may be aspirated for quantitative bacterial cultures, and, if indicated, for diagnosis of small intestinal bacterial overgrowth and pancreatic insufficiency.

However, many primary etiologies of neonatal diarrhoea have been identified and we briefly summarize them.

Congenital diarrhoeal disorders

Congenital diarrhoeal disorders (CDDs) are a group of rare severe enteropathies [3]. Most CDDs display a similar clinical presentation despite a different outcome. Therapy should be started soon to prevent life-threatening complications [19].

We recently proposed a classification of CDDs that includes four groups:

i) defects in digestion, absorption and transport of nutrients and electrolytes;
ii) disorders of enterocyte differentiation and polarization;
iii) defects of enteroendocrine cell differentiation;
iv) disregulation of the intestinal immune response.

CDDs are inherited and in most cases the genetic defect is known [19]. However, a specific CDD is only rarely diagnosed based on clinical features, when diarrhoea is a symptom of a more complex syndrome. Furthermore, milder forms of CDDs may remain undiagnosed until adulthood. Therefore molecular analysis may contribute to rapid and unequivocal diagnosis in a high percentage of CDDs, and for many frequent disorders, molecular analysis is commercially available [19]. In the majority of cases, genes responsible for CDD are not particularly large, which allows scanning techniques like gene sequencing for molecular analysis. Furthermore, selected CDDs in specific ethnic groups are caused by a single mutation due to the founder effect, while the same diseases in other ethnic groups may be due to myriad of different mutations. Among all the diseases listed in Table 7, molecular diagnosis can be routinely performed in most, except: (i) congenital MGD, because no mutations have been identified so far in the putative disease gene MGAM in affected patients, suggesting that the disease may depend on other regulatory genes; (ii) FM, in which more genes encoding fructose carriers may be involved; (iii) CSD, in which only syndromic forms have mutations in the SPINT2 gene; (iv) IPEX-like syndrome, for which the disease gene is still unknown even if a single patient had a mutation in the CD25 encoding gene [19]. In some CDDs, like GGM, IPEX, CF and molecular analysis has been used for prenatal diagnosis; given the severe outcome of most CDD, and the availability of effective gene scanning, the request for prenatal diagnosis will increase. Prenatal diagnosis should always be associated with multidisciplinary counselling to the families [19].

The total number of CDDs has gradually increased, but the incidence of most of them remains to be established. Apart from the fructose malabsorption (FM) that in Western countries involves up to 40% of subjects, CDDs are rare [20]. In fact, their incidence ranges between 1:2500 (CF) to 1:5000 (sucrase-isomaltase deficiency, SID) to 1:60.000 (congenital lactase deficiency, LD) up to 1:400,000 (Tricho-Hepato-Enteric, THE syndrome) [21]. For other CDDs, such as polyendocrinopathy, X-linked (IPEX) syndrome or autoimmune polyglandular syndrome type 1 (APS1), few cases have been described so far, but the recent identification of the disease-genes and the availability of molecular analysis may reveal a higher incidence [22]. Furthermore, selected CDDs are more frequent in ethnic groups where consanguineous marriages are common, or in some geographic areas due to founder effects. For example, congenital LD is particularly frequent in Finland; lysinuric protein intolerance (LPI) has a higher incidence either in Finland and in Japan due to founder effect, and a specific mutation is typically found in each of the two ethnic groups; in southern Italy there are several affected patients, related to four different kindreds [23]; congenital SID (whose incidence is 1:5000 worldwide) may affect up to 5% of the population in Greenland, Alaska and Canada [24]. Similarly, CLD is sporadic worldwide and a large genetic heterogeneity has been reported in the approximately 150 patients described so far [25] Even if most CDDs are rare, a recent nationwide Italian study estimated an overall occurrence rate of one per 2000 hospitalized newborns [10]; immune response and altered enterocyte differentiation and polarization were the most common etiologies [26].

Molecular analysis has changed the diagnostic approach to CDD, leading to a reduction of invasive and expensive procedures. However, some critical points remain: (i) the molecular analysis should be based on scanning procedures [27], including the search for large gene deletions [28], using adequate quality control programs [29] and well trained technologists; (ii) functional analysis of novel mutations is needed to demonstrate their pathogenic role; (iii) the negative results of molecular analysis does not exclude the disease, because mutations may involve non-coding, regulatory areas; high throughput sequencing could help to perform extensive analyses; however, also if the mutation is not known, carrier and prenatal diagnosis may be performed using linkage analysis; (iv) some CDD are very rare; it is necessary that laboratories offer molecular diagnosis also for such 'orphan' diseases.

Therapeutic approach to chronic diarrhoea in children

Chronic diarrhoea associated with impaired nutritional status is serious, and therapy should be started promptly. Treatment includes general supportive measures, nutritional rehabilitation, elimination diets and some drugs. Proabsorptive drugs or hormones (GH, serotonin analogues, acetorphane), are used for promoting restoration of disrupted intestinal epithelium.

Nutritional rehabilitation is often essential and is based on clinical and biochemical assessment. In moderate to severe malnutrition, caloric intake may be progressively increased to 50% or more above

Table 7
Inheritance, epidemiology and pathological mechanisms of congenital diarrhoeal disease.

Disease	Gene		Transmission and incidence	Mechanism
	Name	Location		
1) Genes encoding brush-border enzymes				
Congenital lactase deficiency (LD)	LCT	2q21.3	AR, 1:60.000 in Finland; lower in other ethnic groups	Osmotic
Congenital sucrase-isomaltase deficiency (SID)	SI	3q26.1	AR, 1:5.000; higher incidence in Greenland, Alaska and Canada	Osmotic
Congenital maltase-glucomaylasedeficiency (MGD)	not defined	--	few cases described	Osmotic
2) *Genes encoding membrane carriers*				
Glucose-galactosemalabsorption (GGM)	SLC5A1	22q13.1	AR, few hundred cases described	Osmotic
Fructose malabsorption (FM)	not defined	--	up to 40%	Osmotic
Fanconi-Bickel syndrome (FBS)	SLC2A2	3q26.2	AR, rare, higher frequency in consanguineous	Osmotic
Acrodermatitisenteropathica (ADE)	SLC39A4	8q24.3	AR, 1:500.000	Osmotic
Congenitalchloridediarrhea (CCD, DIAR 1)	SLC26A3	7q31.1	AR, sporadic; frequent in some ethnies	Osmotic
Lysinuric protein intolerance (LPI)	SLC7A7	14q11.2	AR, about 1:60.000 in Finland and in Japan; rare in other ethnic groups	Osmotic
Primary bile acid malabsorption (PBAM)	SLC10A2	13q33.1	AR	Secretory
Cystic fibrosis (CF)	CFTR	7q31.2	AR, 1:2.500	Osmotic
3) *Genes encoding pancreatic enzymes*				
Enterokinase deficiency (EKD)	PRSS7	21q21	AR	Osmotic
Hereditary pancreatitis (HP)	PRSS1 SPINK1	7q34 5q32	AR, cases with compound mutations in different genes; SPINK1 mutations may also cause tropical pancreatitis	Osmotic
Congenital absence of pancreatic lipase (APL)	PNLIP	10q25.3	--	Osmotic
4) Genes encoding proteins of lipoprotein metabolism				
Abetalipoproteinemia (ALP)	MTTP	4q27	AR, about 100 cases described; higher frequency among Ashkenazi	Osmotic
Hypobetalipoproteinemia (HLP)	Apo B	2p24.1	autosomal co-dominant	Osmotic
Chilomicron retention disease (CRD)	SAR1B	5q31.1	AR, about 40 cases described	Osmotic
5) *Genes encoding other typeof proteins*				
Congenital sodium diarrhea (CSD, DIAR 3)	SPINT2 (only syndromic CSD)	19q13.2	AR	Osmotic
Shwachman-Diamond syndrome (SDS)	SBDS	7q11	AR	Osmotic

Table 7 (*continued*)

2)Defects of enterocyte differentiation and polarization

Disease	OMIM number	Transmission and incidence	Mechanism
Microvillous Inclusion Disease (MVID, DIAR 2)	251850	AR; rare; higher frequency among Navajo	Secretory
Congenital tufting enteropathy (CTE, DIAR 5)	613217	AR; 1:50-100.000; higher among Arabians	Secretory
Tricho-Hepato-Enteric sindrome (THE)	222470	AR, 1:400.000	Secretory

3)Defects of enteroendocrine cells differentiation

Disease	OMIM number	Transmission and incidence	Mechanism
Congenital malabsorptivediarrhea (CMD, DIAR 4)	610370	AR; few cases described	Osmotic
Proprotein convertase 1/3 deficiency (PCD)	600955	AR	Osmotic

4)Defects of modulation of intestinal immune response

Disease	OMIM number	Transmission and incidence	Mechanism
Autoimmune polyglandular syndrome type 1 (APS1)	240300	AR; AD (1 family)	Secretory
Immune dysfunction, polyendocrinopathy, X-linked (IPEX)	601410	X linked (autosomal cases described), very rare	Secretory
IPEX-like syndrome	--	not X-linked	Secretory

Modified from reference [19] with author's permission: Terrin G, Tomaiuolo R, Passariello A, Elce A, Amato F, Di Costanzo M, et al. Congenital diarrhoeal disorders: an updated diagnostic approach. Int J Mol Sci 2012;13:4168–85.

the recommended dietary allowances. The intestinal absorptive capacity should be monitored by digestive function tests. In children with steatorrhoea, medium chain triglycerides may be the main source of lipids. Lactose-free diet should be started in all children with chronic diarrhoea, as recommended by the WHO [30]. Lactose is generally replaced by maltodextrin or a combination of complex carbohydrates. Sucrose-free formula is indicated in sucrase-isomaltase deficiency. Semi-elemental or elemental diets have the dual purpose of overcoming food intolerance, which may be the primary cause of chronic diarrhoea in infants and young children as well as facilitating nutrient absorption. The sequence of elimination should be graded from less to more restricted diets, i.e. cow's milk protein hydrolysate to amino-acid-based formula, depending on the child's condition. In severely compromised infants it may be reasonable to start with amino-acids-based feeding.

Clinical nutrition can include enteral or parenteral nutrition [31] Enteral nutrition may be performed via nasogastric or gastrostomy tube, and is indicated in a child who is not able to be fed through the oral route, either because of primary intestinal diseases or because of extreme weakness. Continuous enteral nutrition is effective in children with a reduced absorptive function, such as short bowel syndrome, since it extends the time of nutrient absorption through the still functioning surface area. In extreme wasting, enteral nutrition may not be sufficient and parenteral nutrition is required.

Micronutrient and vitamin supplementation are part of nutritional rehabilitation and prevent further problems, especially in malnourished children from developing countries [32]. Zinc supplementation is an important factor in both prevention and therapy of chronic diarrhoea, since it

promotes ion absorption, restores epithelial proliferation and stimulates immune response. Nutritional rehabilitation has a general beneficial effect on the patient's general condition, intestinal function, and immune response.

Drug therapy includes anti-infectious drugs, immune suppression, and drugs that inhibit fluid loss and promote cell growth. If a bacterial agent is detected, specific antibiotics should be prescribed. Empiric antibiotic therapy may be used in children with either small bowel bacterial overgrowth or with suspected bacterial or parasitic diarrhoea. In Rotavirus-induced severe and protracted diarrhoea, oral administration of human immunoglobulins (300 mg/kg) should be considered [33].

Immune suppression should be considered in selected conditions such as autoimmune enteropathy. Treatment may be also directed at modifying specific pathophysiologic processes [34]. Severe ion secretion may be reduced by pro-absorptive agents, such as the enkephalinase inhibitor racecadotril. In diarrhoea due to neuroendocrine tumours, microvillus inclusion disease and enterotoxin-induced severe diarrhoea, a trial with somatostatin analogue octreotide may be considered. Zinc and growth hormone promote both enterocyte growth and ion absorption and may be effective when intestinal atrophy and ion secretion are associated. Butyrate has been proposed for the treatment of congenital chloride diarrhoea [35]. However, when other attempts have failed, the only option may be parenteral nutrition or intestinal transplantation [36].

Conclusions

The etiologies of chronic diarrhoea in children are different from adults. It requires a specific diagnostic approach, determined by age and clinical conditions to guide evaluation.

The initial diagnostic approach should be noninvasive and guided by tests that drive the need and the type of more invasive investigations. Treatment is substantially different with a relatively major role of nutritional interventions that are essential in a growing child, and to prevent or stop the vicious cycle of diarrhoea and malnutrition.

Practice agenda

- The aetiology and clinical presentation of chronic diarrhoea in children are different from that observed in adults;
- The diagnostic approach should be noninvasive and driven by intestinal function tests;
- Nutrition has a major role in the treatment of chronic diarrhoea. It includes both nutritional rehabilitation in malnourished children and exclusion diet in food intolerance.

Research agenda

- Validated noninvasive tests to assess the intestinal function and inflammation are strongly needed.
- Genetic analysis needs to be developed for a better knowledge of etiologies of congenital diarrhoea
- The role of intestinal pathogens in chronic diarrhoea, and biomarkers to monitor its course, should be investigated.

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